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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 11/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/664,991	BJELDANES ET AL.	
	Examiner	Art Unit	
	Timothy E. Betton	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *20-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-19 are currently pending and are the subject of this Office Action. Applicants' have withdrawn claims 8-14 and 20-22 in response to Examiner's Restriction Requirement mailed 25 September 2006. However, all claims are under examination, which include at least one embodiment of the **elected DIM compound**. Thus, claims 1-14 are also under examination (because of disclosure of at least one embodiment of the elected DIM compound), as being elected, along with claims 15-19.

Election/Restrictions

Applicants' election of a single core species: (a) 3,3"(DIM), wherein R1-R7 and R1'- R7' are hydrogen in the reply filed on 9 October 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claim Rejections – 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter, which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants' use of the term 'determined' is unclear in regard to a proper encompassing assessment and understanding of the manner and process of using. The specification does not yield a proper written description of the term 'determined' in relation to the claimed invention. Instant claim 17 is vague in its description of 'determined', only disclosing a manner of description of said term based upon disclosed disease states, i.e., prostate hyperplasia, acne, androgenetic alopecia and hirsutism. The specification fails to properly disclose what the determination is based upon independent of alleged disease states disclosed. Examples of proper determination would be descriptive standards of determination, protocols, documented cooperative agreements (amongst healthcare coordinators, physicians, pharmacists) etc.

The phrase "determined to be subject or predisposed to an androgen-dependent pathology" is vague and unclear in its explanation. Prostate hyperplasia may be plausible in the broadest reasonable scope in regard to this claimed disclosure. However, conditions such as acne, hirsutism, and alopecia would not necessarily necessitate being predisposed or subject to an androgen-dependent pathology having need of said antiandrogenic agent.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for arresting cancerous prostatic cells *in vitro*, does not reasonably provide enablement for the treatment of androgen-dependent cancers in patients nor the specific treatment of prostate hyperplasia.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As stated in MPEP 2164.01(a), " There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue."

In re Wands , set forth the following eight factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, 1ST paragraph:

1. The nature of the invention;
2. The state of the prior art;
3. The predictability or lack thereof in the art;
4. The amount of direction or guidance present;
5. The presence or absence of working examples;
6. The breadth of the claims;
7. The quantity of experimentation needed; and
8. The level of the skill in the art.

The nature of the invention

The invention is drawn to a method of "providing an antiandrogen to a host", using the compounds found in claims 15-19. Claim 18 and 19 further narrow "cancer" by specifying "prostate cancer."

The state of the prior art and the predictability or lack thereof in the art

The state of the art, pharmacology, involves screening *in vitro* and *in vivo* in order to determine which compounds exhibit pharmacological activities. There

is no absolute predictability even in view of the seemingly high level of skill in the art.

Because of the nature of unpredictability, it is highly unlikely that the contemporary knowledge in the art would allow one of ordinary skill in the art to accept that the instantly claimed compounds or pharmaceutical compositions thereof are capable of treating cancer broadly in any particular patient.

The amount of direction or guidance present and presence or absence of working examples

There is referenced direction or guidance in Applicants' specification for a method of providing an antiandrogen to a host. However, *Exemplary Empirical Protocols* (page 9 of specification) establish only a general structure of the claimed scope of the invention.

Pages 9-21 of Applicants' specification reference *in vitro* assays showing applicants' claimed compounds' ability to arrest prostate cancer cells. However, Applicants' specification fails to provide support for the use of applicants' claimed invention in the treatment of said condition in patients, as disclosed in claims 15-19.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Those of skill in the art recognize that *in vitro* assays and/or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical

correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state.

Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p. 4; reference to USPN 7011951 and USPN 5518915) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This result has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro).

Further, Dermer (Bio/Technology, 1994, 12:320; reference to Oncology Reports 10: pgs 783-789, 2003) teaches that, petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the

human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary-type step to enable the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. It is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

In view of the teachings above and the lack of guidance, workable examples and or exemplification in the specification, it would require undue experimentation by one of skill in the art to determine with any predictability, that the method would function as claimed.

Claim Rejections – 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3-6 and 16-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "reduction" directed toward instant claims 3-6 and 16-19 is a relative term, which renders the claim indefinite. The term "reduction" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Applicant must provide a proper definitive meaning by what the term "reduction" is thereby referenced. Said term does not necessarily connote improvement or intended treatment if there are no standards by which to judge proper and appropriate treatment or palliation. The measure, order, and degree of the term "reduction" must be properly disclosed in the claims as well as the specification.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 are rejected under 35 U.S.C. 103(a) as being obvious over Firestone *et al.,* (USPN 6001868) in view of Safe (PG PUB: US 20020115708 A1).

The applied references have a common claimed invention and/or method steps with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified

under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims are drawn to methods of providing an antiandrogen to a host; the method comprising the steps of: **(a) contacting** the host with an effective amount of an antiandrogenic, optionally substituted 3,3'- (DIM) and **(b) detecting** a resultant antiandrogenic response in the host.

Firestone *et al.,* disclose an invention that provides methods and compositions related to novel bioactive derivatives of indole-3-carbinol (e.g., (DIM)). It further teaches a method by way a target cell is **contacted** with disclosed compound under conditions whereby the growth of the target cell inhibited. Furthermore, Firestone *et al.*, teach a method of **detecting** via **evaluating** the growth inhibitory activity, **contacting** a cell with an effective amount of the compound and measuring the CDK6 expression in the cell (Abstract, patented claim 2).

Firestone *et al.*, do not disclose the said antiandrogenic agent being used for androgen-dependent pathologies.

Instead, said reference teaches said practicing method(s) on estrogen-dependent pathologies with use of core derivatives of indole-3-carbinol (DIM).

However, Safe discloses the directed use of DIM and derivatives thereof for the specific contacting, detecting, and inhibiting via a gel mobility shift assay for **prostate cancer cells** (Brief description of Drawings – Table CWU – DRTL (1)) in a comparative study to estrogen-dependent pathologies. Safe further discloses the practicing methods of administering said antiandrogenic agent in

published claims 16,34,51, and 69. The motivation of Safe obviated by Firestone *et al.*, therefore promotes the necessity to combine in light of claimed invention.

Firestone et al. teach methods and compositions relating to novel bioactive derivatives of indole-3-carbinol (I3C), which are related to (DIM) in instant application in regard to general structure and mechanism of action. Firestone further teaches the methods of inhibiting targeted cell growth by **(a)** contacting, **(b)** evaluating, and **(c)** measuring the CDK6 expression in the cell in correlation with the growth inhibitory activity of the compound.

Firestone et al. does not teach the identical methods and/or processes which are disclosed in instant application. Additionally, Firestone et al., concentrates on a specific component of the infected cell (CDK6 protein levels), however said reference does contain similar process methods for assaying.

Safe teaches derivatives of the practicing DIM core structure that are also taught in the instant application. In said referenced publication on page 3, section [0039] under the heading: *Definitions*, said structure is disclosed. Derivatives of the core structure are disclosed in the instant application on page 3 of the specification under the heading: *Summary of Invention*. Safe discloses in published claims, the *in vitro* method (by use of assays which are disclosed empirical series of method steps used to detect a reaction) of treating cancer, the method comprising obtaining a mammal comprising cancer cells, and administering to the mammal a composition comprising an effective dose of a compound of the said formula. Published claims 16, 34, 51, and 69 further obviate instant application claims 17-19 using this related core structure in the

use of treatment against the specific cancer-types, i.e., **prostate cancer** and pathologies thereof.

Safe teaches **detection** on page 5, Example 2, section [0058] in that a process is disclosed where inhibition was determined, i.e., where clear proliferation of cancer cell lines were significantly inhibited. Further, detection is implied in said reference where sensitive cells were noticeably inhibited at the lowest concentration.

Detection is defined as: **a)** the act of discovery and/or **b)** in **chromatography**, visualization of the separated material (Stedman's Medical Dictionary, 27th Edition). Chromatography is further defined as the separation of chemical substances and particles by differential movement through a two-phase system. The mixture of materials to be separated is percolated through a column or sheet of some suitable chosen absorbent; the substances least absorbed are least retarded and emerge the earliest; those more strongly absorbed emerge later. Chromatography is also synonymous with absorption.

Safe, in accordance, more specifically teaches **detection** on page 4, section [0047] of said referenced publication where resolution of the mixture using chiral chromatography column would result in the isolation of purified or pure enantiomers products. Furthermore, Safe teaches the use of thin-layer chromatography and liquid chromatography in section [0067] (page 6), both well-established detection methods and/or detection facilitators.

Safe, however, does not teach the specific method of providing said agents for exclusively an antiandrogenic response. Nonetheless, the motivation

to combine both references would have been obvious and proper to one of ordinary skill due to overlap of core compounds, assaying methods, and goal of regimen.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the methods disclosed in Firestone *et al.*, to inhibit via evaluating, contacting, and measuring. It is well known in the art that 13C and DIM (a predominant conversion product of I3C) are potent antiandrogenic agent, effective against androgenic – dependent and/or independent pathologies. It would have been obvious to combine that which is taught in both said references above. DIM and related compounds may be not only chemopreventive, but also act as antitumorigenic agents for bladder and other cancers through the aryl hydrocarbon receptor (AhR) and possibly other mechanistic pathways as evidenced by Safe.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over patented claims 1-3 of U.S. Patent No. 6001868. Although the conflicting claims are not identical, they are not patently distinct from each other because one of ordinary skill in the pertinent art could readily conclude that the term "detecting" is interchangeable with the process of measuring and evaluating as disclosed in patented claims. Both the patented reference and the instant application teach the method of screening or assaying. Assaying contains a number of method steps that are a series of empirical detection processes, with functions that may vary but are interchangeable due to substantial and similar well-established protocols. Therefore, patented claims 1-3 teach an assaying process of **a)** contacting a cell with an effective amount of an I3C derivative, **b)** measuring expression in contacted cell, and **c)** evaluating said activity. The phrase "detecting a resultant antiandrogenic response in host" found in instant claim 1 directly after the contacting step could be reasonably interchangeable with the practicing terms: measuring expression and evaluation of such activity. Assays are implemented in order to detect a reaction. Detection is a form of measurable recognition of a signal and it's specificity and rate of degree and occurrence.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ardin H. Marschel 11/20/06

TEB

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER